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Cardiopulmonary radiation damage

ACE inhibition attenuates radiation-induced cardiopulmonary damage



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ABSTRACT

Background and purpose: In thoracic irradiation, the maximum radiation dose is restricted by the risk of radiation-induced cardiopulmonary damage and dysfunction limiting tumor control. We showed that radiation-induced sub-clinical cardiac damage and lung damage in rats mutually interact and that combined irradiation intensifies cardiopulmonary toxicity. Unfortunately, current clinical practice does not include preventative measures to attenuate radiation-induced lung or cardiac toxicity. Here, we investigate the effects of the ACE inhibitor captopril on radiation-induced cardiopulmonary damage.

Material and methods: After local irradiation of rat heart and/or lungs captopril was administered orally. Cardiopulmonary performance was assessed using biweekly breathing rate measurements. At 8 weeks post-irradiation, cardiac hemodynamics were measured, CT scans and histopathology were analyzed.

Results: Captopril significantly improved breathing rate and cardiopulmonary density/structure, but only when the heart was included in the radiation field. Consistently, captopril reduced radiation-induced pleural and pericardial effusion and cardiac fibrosis, resulting in an improved left ventricular end-diastolic pressure only in the heart-irradiated groups.

Conclusion: Captopril improves cardiopulmonary morphology and function by reducing acute cardiac damage, a risk factor in the development of radiation-induced cardiopulmonary toxicity. ACE inhibition should be evaluated as a strategy to reduce cardiopulmonary complications induced by radiotherapy to the thoracic area.

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Thoracic tumors are among the most common human malignancies [1]. The treatment of choice often includes radiation therapy. Unfortunately, the radiation dose that can be safely administered to the tumor is limited by the risk of radiation-induced toxicity of the surrounding tissues.

The radiation dose emitted to the heart following radiotherapy is of particular concern [2,3]. Specifically, the prevalence of late onset heart failure has been reported including accelerated atherosclerosis, pericardial and myocardial fibrosis, conduction abnormalities, and injury to cardiac valves [4,5]. Both incidence and severity of radiation-induced heart toxicity (RIHT) increase with higher radiation doses, larger volumes exposed, a younger age at time of exposure, and greater time elapse following treatment [6]. In addition, the absolute radiation-related risk for a major

cardiac event is far greater with pre-existing cardiac risk factors or ischemic cardiac disease in women treated for breast cancer. Unfortunately, even with the most advanced photon techniques most women still receive doses of greater than 1–5 Gy to the heart [3].

Interestingly, the risk of radiation-induced lung toxicity (RILT), another potentially life-threatening side effect of radiotherapy of thoracic tumors [7], is enhanced when pre-existing cardiac disease exists [8] and the heart is co-irradiated [9–13]. RILT traditionally is divided into an early inflammatory phase, termed “radiation pneumonitis”, and a late fibro productive phase, termed “fibrosis”. Recently, in a preclinical model, we found that, in concert with inflammation, radiation-induced vascular remodeling played a major role in the etiology of early RILT [14]. It was shown that lung irradiation induced early pulmonary vascular remodeling which resulted in pulmonary hypertension and right ventricle (RV) hypertrophy which eventually lead to cardiopulmonary dysfunction. Additionally, heart irradiation may cause an increased left ventricular (LV) end-diastolic pressure, perivascular fibrosis and consequential pulmonary edema [15]. Although RIHT is regarded as a late side effect of radiotherapy, these recent preclinical

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and clinical [16] findings show that radiation can also affect hearts function early after irradiation, albeit without apparent clinical symptoms. As such, both lung and heart irradiation can cause pulmonary and cardiac toxicity through different mechanisms which consequentially lead to an intensified loss of cardiopulmonary performance after combined irradiation [15]. Our experimental set-up presented herein allows for accurate proton irradiation of specific lung sub-volumes and the heart, and provides a model where early, previously unnoticed subclinical cardiac damage can be visualized. Using the interaction between lung and cardiac damage, we are able to study the physiological mechanism and potential mitigation of early subclinical cardiac damage that is potentially responsible for the development of late symptomatic damage.

Inhibition of the renin-angiotensin system (RAS) seems to be an alluring strategy for attenuating radiation-induced cardiopulmonary dysfunction. There is overwhelming evidence implicating ACE inhibitors in the protection from adverse cardiac remodeling and heart failure development [17]. Moreover, it is known that RAS plays a role in cardiac remodeling and interstitial fibrosis [18]. Interestingly, preclinical studies indicate that suppression of the RAS may ameliorate radiation-induced toxicity in different organs like the kidneys [19], the central nervous system [20] and lungs [21,22]. However, in the latter study interaction with cardiac damage after whole thorax irradiation was not assessed. Therefore, in the current study we aim to investigate the effect of ACE inhibition on early radiation-induced heart damage.

Materials and methods

See [Supplementary data](#) for complete materials and methods.

Animals

The animals used in the experiments were adult male albino Wistar rats of the Hsd/Cpb:WU strain. The experiments were performed in agreement with the Netherlands Experiments on Animals Act (1977) and the European Convention for the Protection of Vertebrate Animals Used for Experimental Purposes (Strasbourg, 18.III.1986).

Local lung and heart irradiation

To induce cardiopulmonary damage, rat hearts, lungs, or both were irradiated to 20 Gy (single fraction) using the shoot-through technique with 150 MeV protons from the cyclotron at the Kernfysisch Versneller Instituut, as published previously [9,11,23,24]. Rats were given captopril in the drinking water with a daily dose of 30–60 mg/kg body mass, comparable with that given clinically. The animals (sham) treated with captopril were observed for 3 months after irradiation to determine cardiopulmonary function, structure and molecular changes as described below.

Breathing rate assay

To assess response of cardiopulmonary function to radiation, breathing rate (BR) was measured before and every two weeks after the irradiations up to week 12, as previously described [10,23].

CT imaging

Local density changes were assessed using CT imaging 8 weeks after irradiation. The CT images were analyzed with our recently developed highly-sensitive CT analysis method [25].

Cardiac hemodynamic measurements

To investigate the cardiac physiological changes early after heart and/or lung irradiation, LV or RV hemodynamic measurements were carried out 8 weeks after irradiation. For LV measurements the recorded parameters included LV end-diastolic and end-systolic pressure (LVEDP and LVESP), dp/dtmax (maximum rate of LV pressure change), dp/dtmin (minimum rate of LV pressure change) and Tau (LV relaxation constant). For RV hemodynamic measurement the right ventricle pressure (RVP) and pulmonary artery pressure (PAP) were recorded.

Histopathology

Sections of the rat lungs, LV, RV and intraventricular septum (IVS) were stained with Hematoxylin & Eosin (HE) and Masson's Trichrome (MT) and analyzed morphologically for signs of parenchymal and vascular damage or cardiac damage, respectively.

Quantitative polymerase chain reaction (QPCR)

Total RNA was extracted from the heart LVs and mRNA levels of ANP and BNP were measured by QPCR.

Statistical analysis

Data are expressed as mean values (means \pm SEM). Statistical analyses were performed using the two-way repeated measures ANOVA followed by the *post hoc* Tukey or Bonferroni correction for multiple comparisons and the log-rank (Mantel–Cox) to compare distributions of two groups. Correlational analyses were performed using the Pearson correlation coefficient. In all statistical analyses, significance was defined as $P < 0.05$.

Results

Captopril decreases structural and functional damage in irradiated hearts

To study the influence of ACE inhibition on early radiation-induced cardiac damage, we first investigated the effect of captopril on cardiac structure and function. Rat hearts were irradiated (HIR) ([Supplementary Fig. S1A](#)), thereafter captopril was administered. We assessed the effect of captopril on irradiation-induced LV perivascular and interstitial fibrosis [15]. Eight weeks after irradiation, perivascular fibrosis developed in the LV, but this was significantly decreased with captopril treatment ([Fig. 1A and B](#)). Moreover, captopril decreased the LV interstitial fibrosis score in HIR as well as in un-irradiated animals ([Fig. 1C and D](#)). Perivascular/interstitial fibrosis is known to be an important factor in the pathophysiological process contributing to diastolic dysfunction by impairing cardiac relaxation [15,17,26]. Therefore, we next investigated whether the observed decrease in LV perivascular and interstitial fibrosis by captopril treatment translated into an improved cardiac diastolic function. Indeed, HIR was associated with increased LVEDP and the LV relaxation constant, Tau, which were both normalized by captopril treatment ([Fig. 1E and F](#)). These effects are independent of any changes in systemic blood pressure, maximum and minimum rates of LV pressure change (dPdtmax and dPdtmin) or changes in LV weight, since these parameters were comparable between captopril and control-treated rats ([Supplementary Fig. S2](#)). The secretion of brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) are stimulated by excessive myocardial stretch [27]. Therefore we assessed BNP and ANP mRNA levels in the irradiated LV by qPCR. HIR lead to increased ANP and BNP mRNA, which appeared to be lowered by captopril treatment, albeit not significantly ([Supplementary Fig. S3A and B](#)).

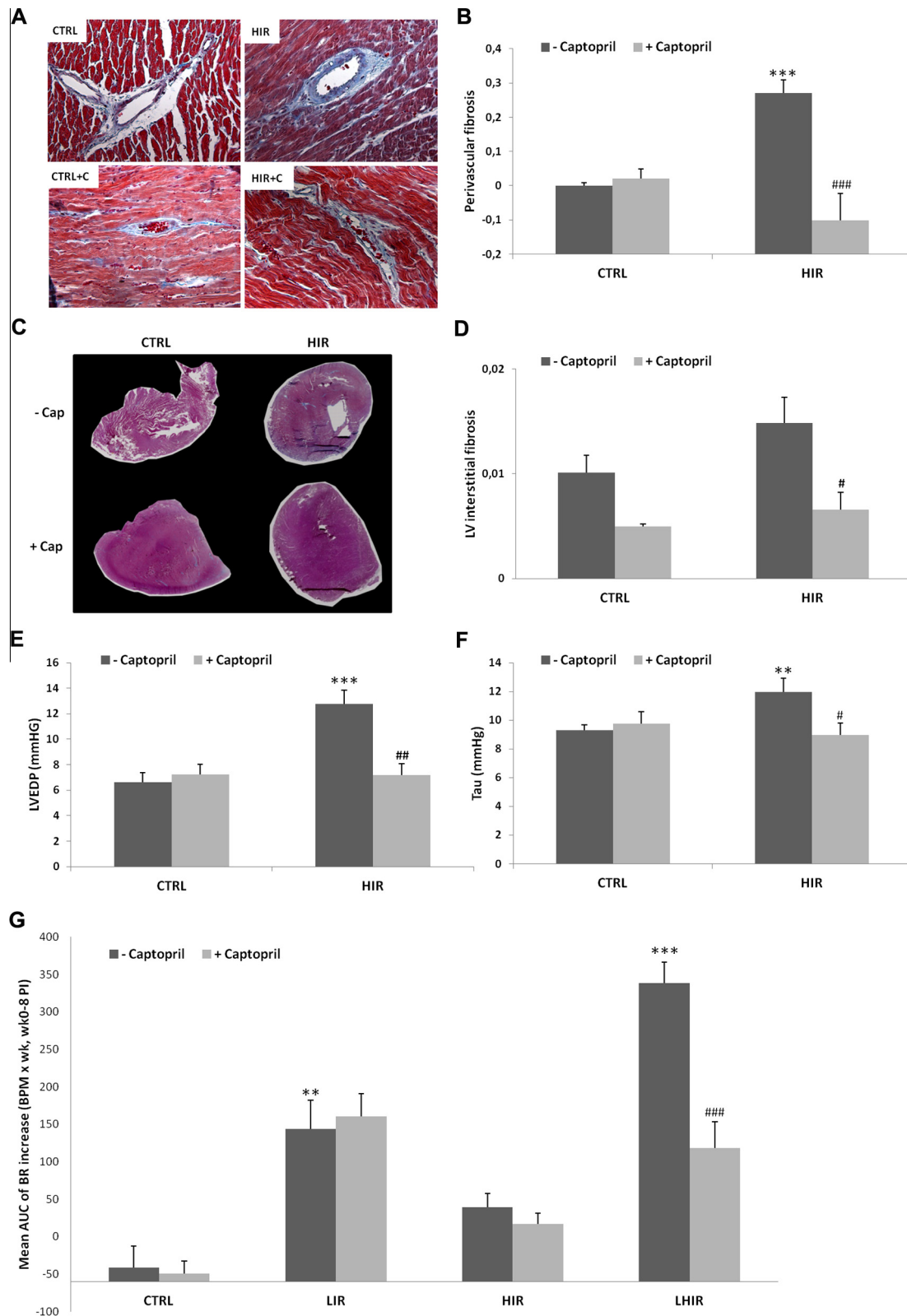


Fig. 1. Captopril decreases structural and functional damage in irradiated hearts. (A and B) Immunohistochemical staining and morphological quantification of perivascular fibrosis and interstitial fibrosis (C and D) in irradiated hearts shows a significant reduction after captopril treatment. Masson trichrome staining was performed: red stain = muscle fiber, blue stain = collagen. Scale bar: 100 μ m. Data are presented as means \pm SEM; $n \geq 3$. (E) Heart irradiation induces LV diastolic dysfunction. This was shown by increased left ventricle end-diastolic pressures (LVEDP). Captopril treatment decreased the elevated pressures after HIR. Data are presented as means \pm SEM; $n \geq 4$. (F) HIR leads to an increased LV relaxation constant Tau. Treatment with captopril leads to a significant decrease of Tau after HIR. Data are presented as mean \pm SEM; $n \geq 4$. (G) Early cardiopulmonary dysfunction was assessed by increase in breathing rate (BR). LIR induces increased BR; captopril treatment did not affect BR. LHIR enhanced BR increase compared to LIR, and captopril attenuated early radiation-induced cardiopulmonary dysfunction in LHIR. Data are presented as mean area under BR increase curve from week 0 to 8 after irradiation: means \pm SEM; $n = 9$. *** $P < .001$, ** $P < .01$ compared with control. ### $P < .001$, ## $P < .01$, # $P < .05$ comparison between \pm captopril treatment. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ACE inhibition ameliorates early radiation-induced cardiopulmonary dysfunction only when the heart is co-irradiated

Since captopril significantly protects against radiation-induced structural and functional cardiac changes, we hypothesized that it should also exert protective effects on the lung [15,28]. Therefore, we next investigated the effect of captopril on cardiopulmonary dysfunction early after irradiation using our non-invasive heart and lung interaction rat model.

We measured BR as a measure of cardiopulmonary function in rats irradiated on the heart, lung, both heart and lung, and treated the animals with captopril including a sham-treated group (see [Supplementary Fig. S4](#)). Captopril treatment following administration of 50% 20 Gy lung irradiation (LIR) ([Supplementary Fig. S1C](#)) resulted in a BR increase of ~40 breaths per minute (bpm) at 6–8 weeks post-irradiation that was similar to the sham-treated animals ([Supplementary Fig. S5](#)) and as previously described [10]. Indeed, analysis of the area under the curve of the BR increase from week 0 to 8 after irradiation indicated ([Fig. 1G](#)) that captopril did not influence the control and radiation-induced BR increase after LIR.

Next, we investigated the effect of ACE inhibition on BR after cardiac irradiation. As observed in our previous experiments, HIR does not significantly affect the BR nor does HIR with captopril treatment ([Fig. 1G](#) and [Supplementary Fig. S5B](#)). However, after combined heart and 50% lung irradiation (LHIR) (see [Supplementary Fig. S1B](#)), captopril significantly reduced the enhanced BR observed after untreated LHIR ([Fig. 1G](#) and [Supplementary Fig. S5B](#)). As such, the enhanced cardiopulmonary dysfunction after inclusion of the heart in the irradiation field was completely diminished after captopril treatment leading to a BR level comparable to the LIR animals. In summary, captopril only ameliorates radiation-induced BR increase when the heart is co-irradiated.

Captopril treatment reduces lung damage measured by CT after (co-)irradiation of the heart

Thoracic irradiation leads to structural changes of heart and lungs. Therefore, we assessed the effect of captopril on these structural changes by using our recently developed CT analysis method [25] which is highly sensitive for non-invasive assessment of thoracic structural changes.

Consistent with the improved cardiopulmonary function, the severe structural changes of the heart and lungs observed after

LHIR were significantly reduced after captopril treatment ([Fig. 2A](#) and [B](#)), and again, this was only observed when the heart was co-irradiated. These structural changes are due to, for example, pleural or cardiac effusion, pulmonary edema, infiltration or fibrosis. Therefore, to further investigate how captopril improves cardiopulmonary function and structure, we visually assessed the presence or absence of effusion. After opening the thorax and diaphragm of the animals, no animals from the LIR group but most of the HIR and LHIR animals presented with effusion in their pleural cavity. Moreover, none of the HIR animals treated with captopril showed signs of pleural effusion. A similar observation was made for pleural effusion after LHIR and captopril treatment ([Fig. 2C](#)). Several animals also presented with pericardial effusion in combination with pleural effusion. LHIR led to pericardial effusion in 6 out of 9 irradiated animals. After captopril treatment, only 1 out of 9 animals presented with pericardial effusion ([Fig. 2C](#)). Pleural and pericardial effusion, known side effects of thoracic irradiation [7,29], were clearly diminished by ACE inhibition.

Captopril treatment decreases RILT only when the heart is (co-)irradiated

We already showed that early radiation-induced damage to cardiac structures is reduced with captopril treatment which may indirectly lead to less pleural effusion. To study this in more detail we next analyzed lung morphology. Morphologic analysis showed that captopril treatment lead to significantly less alveolar inflammation, infiltrates and early fibrosis after HIR ([Fig. 3A, B and D](#)). After LHIR, captopril treatment significantly reduced inflammation, infiltrates and interstitial edema in the lungs ([Fig. 3A, B and C](#)). These features may explain the decrease of pleural effusion following captopril treatment. Taken together, captopril treatment decreases RILT, but consistent with the previous findings, this effect is observed only when the heart is (co-)irradiated.

ACE inhibition does not protect the pulmonary vasculature after thoracic irradiation

Previously, we found that radiation-induced pulmonary vascular remodeling is an important factor in the development of RILT resulting in pulmonary hypertension and RV hypertrophy that eventually leads to cardiopulmonary dysfunction [14,15]. In

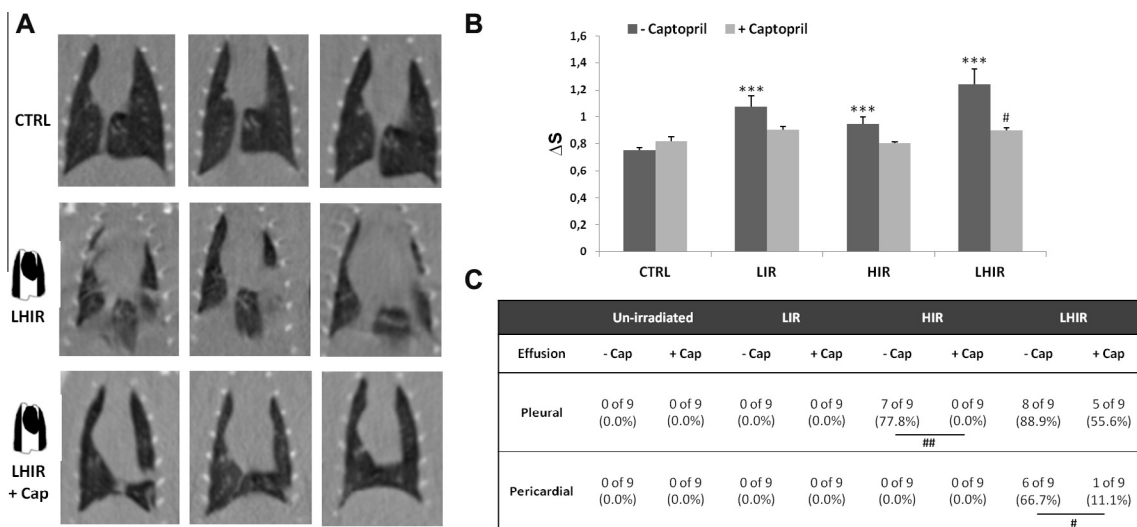


Fig. 2. Captopril treatment improves cardiopulmonary structure after HIR and/or LHIR detected by CT imaging. CT imaging (A) and CT analysis with the ΔS method (B) show that LHIR leads to structural changes in the thorax which improves significantly with captopril treatment. (C) At the peak of early RILT, 8 weeks PI, 7 out of 9 HIR animals presented with pleural fluid in their thoracic cavity, whereas in the captopril-treated group, none of the animals had pleural fluid. Animals with LHIR had pleural effusion (89%) and pericardial effusion (67%), while in captopril-treated animals this was reduced to 56% and 11%, respectively. ΔS data are presented \pm SEM; $n \geq 3$; *** $P < .001$ compared with control. # $P < .05$, ## $P < .01$ comparison between \pm captopril treatment.

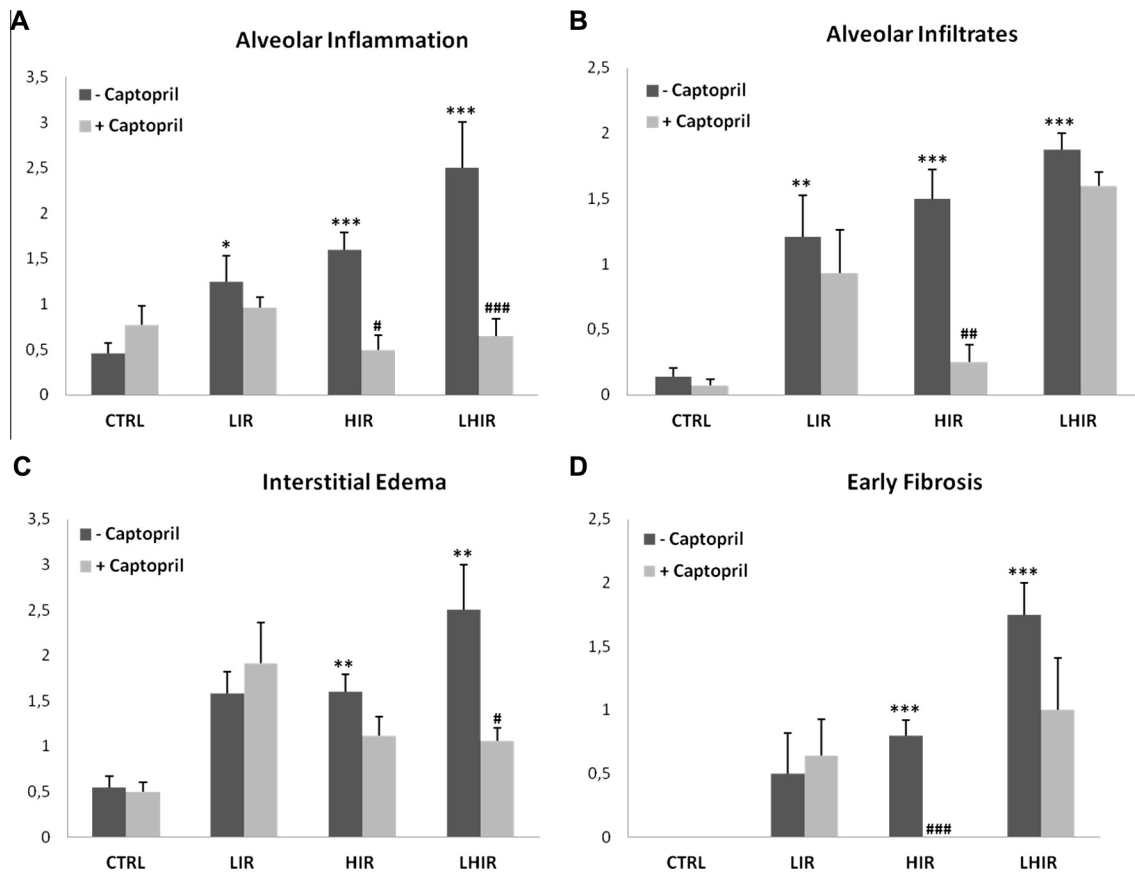


Fig. 3. Lung morphology after LIR, HIR and LHIR with or without captopril treatment. (A) LIR, HIR and LHIR all lead to a significant increase in alveolar inflammation. Captopril significantly reduced inflammation after HIR and LHIR. (B) LIR, HIR and LHIR lead to increased alveolar infiltrates. Captopril treatment significantly decreased infiltration after HIR. (C) HIR and LHIR lead to interstitial edema. Captopril treatment significantly decreased interstitial edema. (D) Early pulmonary fibrosis presented after HIR and LHIR, which was significantly reduced by captopril. Data are presented as means \pm SEM; $n \geq 4$; *** $P < .001$, ** $P < .01$, * $P < .05$ compared with control. ### $P < .001$, ## $P < .01$, # $P < .05$ comparison between \pm captopril treatment.

addition to parenchymal damage, lung irradiation caused vascular damage which also influenced cardiopulmonary function. To this end, we studied the effect of captopril on early radiation-induced pulmonary vascular damage. We analyzed pulmonary vascular remodeling/occlusion, pulmonary artery pressure (PAP) and RV hypertrophy in the non- and captopril-treated animals. Consistent with our previous experiments, LIR, HIR and LHIR lead to vascular remodeling/occlusion in- and out-of the irradiated field indicating a global vascular response in the lungs, while HIR caused vascular remodeling only in the irradiated field (Fig. 4A and B). Captopril treatment did not decrease vascular remodeling. Consistent with this, no differences in PAP or RV hypertrophy were observed (Fig. 4C and D, Supplementary Fig. S6). It therefore appears that although captopril ameliorates cardiopulmonary dysfunction after combined heart and lung irradiation, this cannot be explained by a protective effect on the pulmonary vasculature which is equally damaged in animals with or without captopril.

In summary, these data indicate that captopril solely protects the heart from radiation damage. Captopril treatment attenuated radiation-induced pleural and pericardial and cardiac fibrosis resulting in an improved LVEDP and Tau. In addition, captopril reduced RILT, but only when the heart was co-irradiated.

Discussion

In the current study we show that ACE inhibition attenuated early radiation-induced heart damage and consequentially prevented the influence of dose to the heart on lung toxicity.

Specifically, we show that captopril prevented LV perivascular fibrosis and the elevations in LVEDP induced by heart irradiation, thus, preventing LV diastolic dysfunction and consequent pulmonary damage. RIHT after cancer therapy is generally believed to be a late side effect. However, evidence from our studies [15] as well as other preclinical [30,31] and clinical [32,33] studies suggest that radiation may already exert an early effect on the heart. Although this early effect is subtle and subclinical, it may have detrimental consequences when combined with lung irradiation. Apart from this, it may exert late effects, such as ischemic heart disease/accelerated atherosclerosis, pericardial and myocardial fibrosis, conduction abnormalities, and injury to cardiac valves [4,5]. In our experimental model, captopril reduced the heart component of thoracic irradiation-induced damage, diminishing its effect on total early cardiopulmonary damage which only became clinically discernible when both heart and lung were irradiated.

The ACE inhibitor, captopril, was selected based on previous radiation studies where it was proven to be the most successful thus far in reducing radiation damage to multiple organs [20,34–36].

However, an attenuating effect on the hearts function after irradiation its affect on the heart has not been reported. This is interesting because many studies have shown that cardiac dysfunction other than caused by radiation can be attenuated by ACE inhibition.

Previous studies showed that ACE inhibition has a protective effect on the lung [21,22,34,37] after thoracic irradiation. However, in these studies the heart was always co-irradiated. In the current

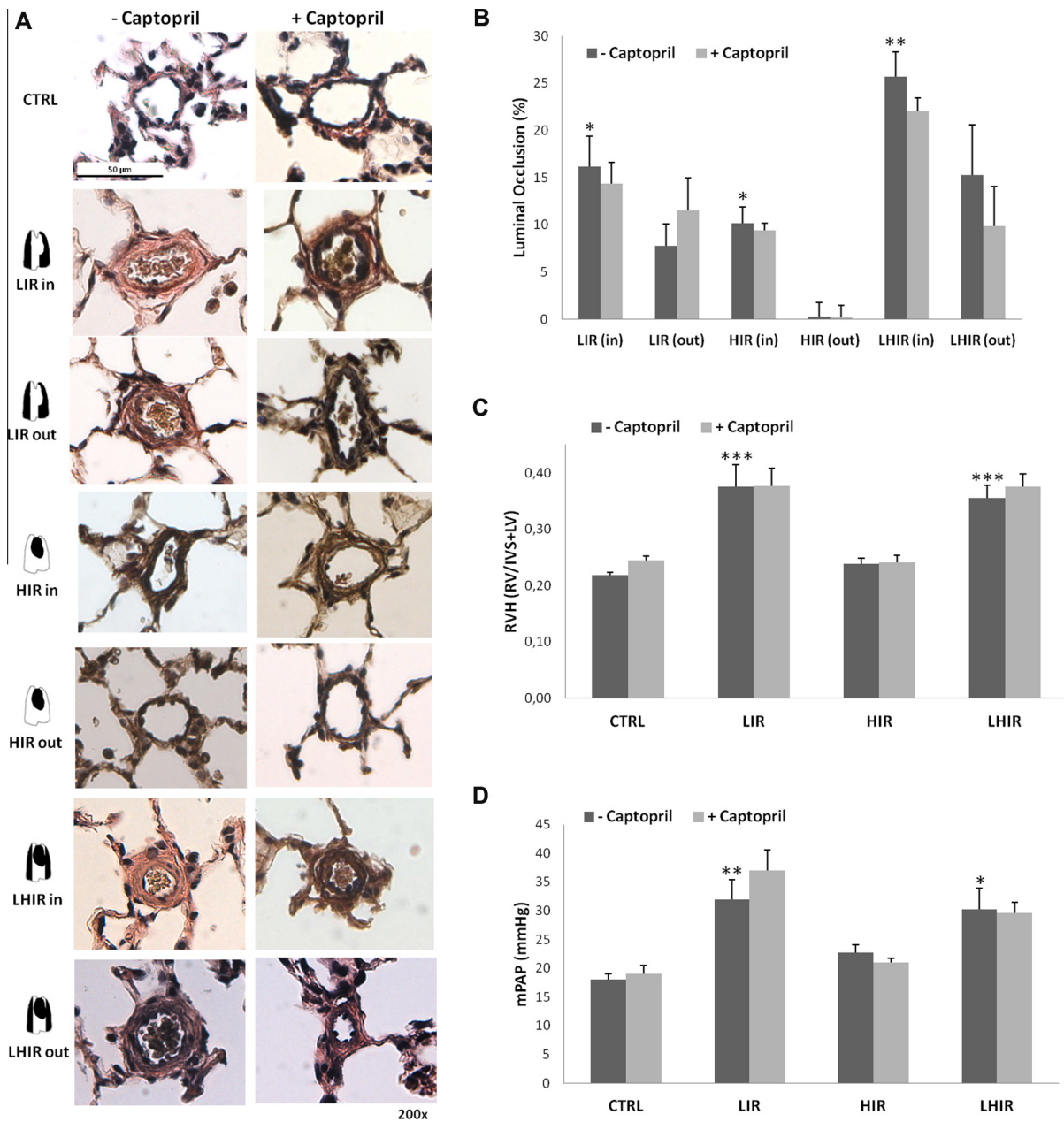


Fig. 4. ACE inhibition does not protect the pulmonary vasculature after thoracic irradiation. (A) Vascular remodeling is present in- and out- of the irradiated field after LIR, HIR and LHIR with or without captopril treatment. (B) Quantification shows a significant increase of luminal occlusion in the irradiated fields of all the groups. Captopril treatment does not change the level of luminal occlusion. The outcome from each group was subtracted from the control group and then presented in the graphs. (C) Captopril does not prevent the development of right ventricle (RV) hypertrophy. The increased workload of the RV leads to right ventricle hypertrophy (RVH) after LIR and LHIR. Captopril showed no effect on the development of RVH in these groups. (D) Captopril had no effect on pulmonary artery pressure after LIR and LHIR. LIR and LHIR lead to an elevated pulmonary artery pressure; no effect of captopril was observed. Data are presented as means \pm SEM; $n \geq 4$; *** $P < .001$, ** $P < .01$, * $P < .05$ compared with control.

study, high precision protons were used instead of photons, which enabled selective irradiation of only the lungs, or virtually only the heart. This helped to elucidate that ACE inhibition does not reduce RILT directly, but rather indirectly by reducing acute heart damage which lead to secondary reductions in pulmonary function loss, inflammation, edema and fibrosis. Apart from their hypotensive action, ACE inhibitors are known to have other properties such as anti-inflammatory action [38]. Further, it has been suggested that the sulfhydryl group in the molecular structure of captopril confers in a free radical scavenger activity, and this can account in part for its radioprotection [39]. It might act as an antioxidant to reduce inflammatory reactive oxygen species and thus mitigate radiation-induced toxicity. In this study it was found that captopril reduced

fibrosis in rat hearts early after irradiation, which in the field of cardiology research is a known property of captopril [40,41].

Reduction of early radiation-induced cardiac fibrosis and consequently cardiac diastolic dysfunction may be of importance for the development of late cardiac damage. Interestingly, radiation-induced myocardial fibrosis that occurs much later can be reduced by captopril [42]. Given that in our model we found ACE inhibition to improve not only cardiac structure, but also function early after irradiation, implicates an important therapeutic application of ACE inhibitors in the field of thoracic radiation oncology that warrants further investigation.

Although many differences exist between our animal studies and radiotherapy in the clinic, for example, single dose versus

fractionation, the presence of patient related co-morbidities, patient pulmonary/cardiac status, and concomitant chemotherapy, there are indications that the same mechanisms might play a role in humans. Both preclinical and clinical studies showed that Ag II may initiate cardiac perivascular fibrosis and diastolic dysfunction [43,44]. Therefore, reduction of fibrosis by ACE inhibition in rats may show reduction in the human heart as well. Moreover, treatment with ACE inhibitors during thoracic irradiation has already shown positive effects, albeit without underpinning the mechanism. Acute respiratory complications and post-radiotherapy radiological changes such as lung consolidation were less likely to develop in lung cancer patients who were treated with ACE inhibitors [37,45]. As in preclinical studies, the dose to the heart was not taken into account in these clinical studies. We therefore propose that retrospective studies be initially performed to compare radiation-toxicity in patients who were or were not receiving ACE inhibitors during their radiation treatment where the heart had been included in the radiation field. This may probably show an even greater protective effect of ACE inhibition when doses to the heart are assessed. To further translate our findings to clinical practice, clinical studies should be performed to investigate whether ACE inhibition exerts the same protective effect on acute radiation-induced heart damage and consequently on RILT as shown in our preclinical study presented herein. Treatment with ACE inhibitors should start directly after irradiation in order to protect against acute heart damage that potentially bears consequences during the later stages of irradiation damage. Since the occurrence of a subsequent cardiac event increases by 7.4% with each gray of radiation to the heart [3], and patients treated for thoracic cancers still receive relevant doses to the heart, it is therefore of great clinical importance to find strategies to reduce this toxicity. Interestingly, ACE inhibitors have been found to not change the radiosensitivity of lung tumor cell lines [46] and even reduce the risk of colorectal cancer [47].

To conclude, ACE inhibition reduces RILT by ameliorating acute cardiac damage. ACE inhibition such as with the clinically-approved agent, captopril, may be a promising strategy to reduce early cardiopulmonary complications induced by radiotherapy to the thoracic area in patients receiving a considerable dose to the heart.

Conflict of interest statement

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2014.11.017>.

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